Attorney's Docket No. 048057/275988 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.:	10/060,697	Confirmation No.: 8553
Applicant(s):	Petersen *et al.*	
Filed:	January 30, 2002	
Art Unit:	1651	
Examiner:	Witz, Jean C.	
Title:	BONE GRAFT SUBSTITUTE COMPOSITION	

Docket No.: 048057/275988
Customer No.: 00826

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF TRANSMITTAL
(PATENT APPLICATION – 37 C.F.R. § 1.192)

1. Transmitted herewith is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on September 15, 2004.

2. ☐ Applicant claims small entity status.

3. Pursuant to 37 C.F.R. § 1.17(c), the fee for filing the Appeal Brief is:
   ☐ small entity $250.00
   ☒ other than small entity$500.00

   Appeal Brief fee due $500.00

   ☒ Any additional fee or refund may be charged to Deposit Account 16-0605.

Respectfully submitted,

Christopher M. Humphrey
Registration No. 43,683

CUSTOMER NO. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

"Express Mail" mailing label number EV 387069988 US
Date of Deposit December 15, 2004

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop Appeal Brief-Patent, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Tracey S. Wright

Attorney's Docket No. 048057/275988 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.:	10/060,697	Confirmation No.: 8553
Applicant(s):	Petersen et al.	
Filed:	January 30, 2002	
Art Unit:	1651	
Examiner:	Witz, Jean C.	
Title:	BONE GRAFT SUBSTITUTE COMPOSITION	

Docket No.: 048057/275988
Customer No.: 00826

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF UNDER 37 CFR § 1.192

This Appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed September 15, 2004.

1. ***Real Party in Interest***

The real party in interest in this appeal is Wright Medical Technology, Inc., the assignee of the above-referenced patent application.

2. ***Related Appeals and Interferences***

There are no related appeals and/or interferences involving this application or its claimed subject matter. For the sake of complete disclosure, however, it is noted that the same combination of references has been used to reject the claims of U.S. Appl. No. 09/947,833, filed September 6, 2001. An appeal brief was filed in this unrelated application on December 3, 2004.

3. ***Status of Claims***

Claims 16-30 are pending and all claims stand rejected as unpatentable over a combination of three prior art references as set forth in greater detail below. The prior art rejection of all pending claims is appealed herein.

4. ***Status of Amendments***

The pending claims have not been amended during prosecution.

5. ***Summary of Claimed Subject Matter***

The present invention is directed to a bone graft substitute composition comprising a calcium sulfate material such as calcium sulfate hemihydrate, demineralized bone matrix, cancellous bone, a plasticizing substance such as carboxymethylcellulose, and a mixing solution, as embodied in independent Claim 16 and Claim 27.

Calcium sulfate in its hemihydrate form is known to chemically react with water to form a hardened material (i.e., to set over time). Applicants have discovered that a plasticizing substance as described in the application serves to disrupt the reaction of calcium sulfate hemihydrate into the hardened dihydrate form, thereby increasing the time it takes for the calcium sulfate to form a hardened composition or completely eliminating the ability of the composition to harden or set. Thus, the present invention provides bone graft compositions that retain a degree of moldability or ejectability for a longer period of time than would be possible with prior art calcium sulfate compositions. In turn, the longer set time provides the clinician with additional time to form the putty or paste into the desired shape matching the bone defect, or additional time to inject the solution using a syringe. Additionally, even in embodiments where the calcium sulfate of the composition is present in a less reactive form, the addition of the plasticizer can impart beneficial handling characteristics, such as improved cohesiveness of the composition, which lessens the tendency of the composition to fall apart when contacted with fluids, and overall better moldability.

6. ***Grounds of Rejection to be Reviewed on Appeal***

Claims 16-30 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of U.S. Patent No. 5,484,601 to O'Leary *et al.*, U.S. Patent No. 5,385,887 to Yim *et al.*, and WO 98/40113 reference listing Wironen as an inventor. The Office Action relies upon the O'Leary reference as teaching a composition comprising demineralized bone powder, an organic liquid carrier and, optionally, a thickening agent such as a cellulosic ester. The Office Action relies upon the Yim reference as disclosing a composition for delivering osteogenic proteins that contains calcium sulfate hemihydrate. The Examiner has taken the position that it would have been obvious to include the calcium sulfate taught in Yim in the composition described in O'Leary because both patents are directed to bone growth promoting compositions and Yim teaches that calcium sulfate improves handling, moldability, and consistency in such a composition. The Examiner relies upon the Wironen reference as disclosing a bone paste that may comprise cancellous bone chips. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to modify the O'Leary composition to include cancellous bone chips based on the teachings of the Wironen reference.

7. ***Argument***

Each argument against the sole prior art rejection of record is set forth below.

There is No Motivation to Combine Yim with O'Leary

Applicants respectfully submit that one of ordinary skill in the art would have no motivation to combine the three references of the rejection in the manner contemplated by the Examiner. Specifically, there is no motivation to combine the calcium sulfate hemihydrate of Yim with the teachings of O'Leary.

The O'Leary reference is directed to a flowable demineralized bone powder composition comprising demineralized bone powder in an organic liquid carrier, such as glycerol. It is clear that this reference is directed to compositions that are intended to maintain a certain consistency for an extended period of time. Although this consistency is described as widely varying, there is nothing in O'Leary to indicate that a composition that hardens or sets over time is envisioned. In fact, the reference suggests otherwise by describing the term "flowable" as including

compositions with consistencies ranging from those that are "shape sustaining but readily deformable . . . to those which are runny" (column 3, lines 30-34). Further, we note that O'Leary suggests the use of a thickener if settling of the bone powder within the organic liquid is a problem. (column 3, lines 56-63). This also suggests that the composition is intended to maintain a liquid, flowable state for an extended period of time. Obviously, if the composition is intended to set into a hardened mass within a short period of time, settling would not be an issue. Additionally, the O'Leary reference suggests that the composition described therein can be prepared "well in advance and stored under sterile conditions until required for use" (column 4, lines 34-37; See also, column 1, lines 63-66). This also suggests that the flowable compositions envisioned by O'Leary maintain a uniform flowable consistency for an extended period of time. Even the Examiner admits in the Advisory Action that the formulation of O'Leary does not "change its state and its moldability is static and does not improve."

All of the above teachings of O'Leary are manifestly inconsistent with the well-known properties of calcium sulfate hemihydrate solutions. As described in the references discussed in the background section of the present application, prior to Applicants' present invention, calcium sulfate hemihydrate was used in certain bone graft compositions where it was understood that the composition would harden or set rather quickly as the calcium sulfate hemihydrate reacted with water to form the dihydrate form. Since it was known in the art that calcium sulfate hemihydrate would cause a composition to harden or set in a relatively short period of time, such as 5-10 minutes, the addition of calcium sulfate hemihydrate to the O'Leary composition would have been avoided by one of skill in the art since the resulting composition would not have been expected to maintain a flowable state for an extended period of time, which is clearly the aim of the reference. Yim itself describes how quickly a calcium sulfate hemihydrate solution loses flowability in Table 2 in column 10. Note that each tested composition appearing in Table 2 was non-flowable within 15 minutes. Better evidence against the combination of O'Leary and Yim could hardly be imagined. The Examiner appears to argue around this point in the Advisory Action by differentiating flowability from moldability and stressing that "a flowable composition may have its moldability improved by the addition of [calcium sulfate hemihydrate]." However, even if this is true, the improvement in moldability will be short-lived and ultimately result in a non-flowable material as described in Yim and other prior art references. A composition that

quickly loses its flowability, even if the loss is accompanied by a short-lived improvement in moldability, is anathema to O'Leary, which clearly envisions a composition that is flowable for an extended period of time, even during storage.

Although Applicants have discovered that the claimed plasticizing substance can forestall the calcium sulfate hemihydrate hardening reaction, this effect is not appreciated in the prior art. Yim purports to suggest compositions including both calcium sulfate hemihydrate and certain cellulosic materials that are described as protein sequestering agents. However, this combination does not appear in any examples and the Yim reference obviously does not appreciate the handling advantages that Applicants have discovered since the reference consistently describes the calcium sulfate hemihydrate as a material that will reduce set-up time and describes numerous compositions in Table 2 that quickly harden or set. As a result, one of ordinary skill in the art without the benefit of Applicants' disclosure would view the combination of calcium sulfate hemihydrate with the O'Leary formulation as likely to negate the flowability requirement set forth in O'Leary. Thus, for this reason, one of ordinary skill in the art would not find the requisite motivation to combine the calcium sulfate hemihydrate of Yim with the O'Leary composition.

Even ignoring the clear suggestion in the art to avoid combining calcium sulfate hemihydrate with O'Leary as discussed above, the Examiner's reasoning for combining Yim with O'Leary is inconsistent with the teachings of the Yim reference. As explained in the after-final office action response, Yim describes the use of calcium sulfate to reduce the preparation time or "set up time" of a composition comprising osteogenic proteins, autogenous blood and a porous particulate polymer matrix material. (column 2, lines 51-65). Presumably, calcium sulfate is useful in this composition to reduce setup time because of the relatively long period of time it takes for autogenous blood to clot in the formulation. Applicants note that this teaching is directly contrary to the present invention since the stated goal in Yim is to reduce set up time, not increase it.

The Examiner relies on language in the Yim reference regarding reduction in set-up time and improvement in handling, moldability and consistency as evidence of a motivation to combine the calcium sulfate hemihydrate of Yim with the formulation of O'Leary. However, as noted above, Yim does not provide a general suggestion that calcium sulfate provides such

advantages in all bone graft compositions. Instead, the Yim reference only suggests that a calcium sulfate hemihydrate-containing substance (CSHS) provides such advantages when combined with the formulation described in U.S. Pat. No. 5,171,579 (see column 2, lines 51-65). Yim only suggests a CSHS provides such advantages in the context of a formulation comprising osteogenic proteins, autogenous blood, and a porous particulate polymer matrix, such as a copolymer of lactic acid and glycolic acid (PLGA). There is no suggestion in the Yim reference that such improved properties would be expected in any other formulation. Yim merely teaches that, "[t]o reduce the preparation time and improve the above formulation's handling characteristics" (emphasis added), a CSHS can be added. The "above formulation" is the formulation described in the '579 patent, which includes an osteogenic protein, autogenous blood, and a porous particulate polymer matrix. Since the composition in the O'Leary reference is not a combination of osteogenic proteins with autogenous blood and a porous particulate polymer matrix such as PLGA, there would be no motivation to combine the CSHS of Yim with the composition described in O'Leary for the reasons suggested by the Examiner. The O'Leary formulation comprises demineralized bone powder and an organic liquid, and such a composition is markedly dissimilar to the composition described in Yim as needing improvement in set-up time, moldability, etc. Further, there is nothing in the O'Leary reference to suggest a problem with moldability, consistency, etc. of the formulation described therein that might lead one of ordinary skill in the art to seek an additive to address such a problem. Indeed, the O'Leary patent seems to suggest that the consistency of the "flowable" material can be adjusted simply by altering the amount of the liquid component (column 3, lines 28-35).

The Examiner responded to this argument in the Advisory Action by noting that Yim describes the addition of calcium sulfate hemihydrate to other compositions as well, such as the suggestion at column 2, lines 27-31 to form a composition containing calcium sulfate hemihydrate and an osteogenic protein. Yet, the Examiner continues to rely on the improved handling/moldability teaching in Yim as the motivating factor for the alleged combination. The Yim reference does not teach that improved handling/moldability will be realized in the other embodiment noted by the Examiner. The osteogenic protein/calcium sulfate hemihydrate embodiment is described more fully at column 8, lines 16-28, where the reference teaches that, in that embodiment, calcium sulfate hemihydrate provides a structural matrix function, an

osteoconductive matrix and a protein sequestering function. There is no discussion of improved handling whatsoever. As Applicants have pointed out, the broad statement by the Examiner in the Advisory Action that "Yim shows that bone repair compositions that do not contain [calcium sulfate hemihydrate] will have improved moldability upon the inclusion of the [calcium sulfate hemihydrate]..." is overbroad and unsupported by the Yim reference. Thus, even ignoring the disincentive to use calcium sulfate hemihydrate in the O'Leary reference described above, the Yim reference fails to provide proper motivation to modify O'Leary in the manner contemplated by the rejection.

As an aside, Applicants dispute the Examiner's assertion in the Advisory Action that Yim teaches four of the five claimed ingredients of Applicants' composition. The Examiner opines that, since demineralized bone matrix can contain bone morphogenic proteins (BMP's), Yim's description of the use of such proteins encompasses demineralized bone matrix. This is simply unsupported by the Yim reference. Although Yim recognizes that BMP's can be isolated from demineralized bone tissue in its background, it clearly only teaches compositions that include isolated BMP solutions. The reference is unequivocal on this point. It is improper to attempt to broaden the unambiguous teachings of Yim to include a suggestion to use demineralized bone matrix. Presumably, if the Examiner felt strongly about this statement, there would be a separate rejection of record that reflected this reading of Yim.

For the reasons set forth above, Applicants respectfully request that the Board overturn the sole rejection or record.

There is No Motivation to Combine Wironen with Yim or O'Leary

In addition, Applicants respectfully submit that there is no motivation to combine the teachings of the Wironen reference with the teachings of either O'Leary or Yim. The Wironen reference describes a bone paste that contains thermally crosslinkable gelatin as the carrier for one or more osteogenic components. The gelatin-based composition has the unique ability to exhibit thermoreversible gelation properties that allow the composition to be a fluid at a temperature above normal body temperature and a solid gel at body temperature (see page 7, line 27- page 8, line 6; page 11, lines 21-26; page 12, lines 9-14). As explained throughout the Wironen reference, the use of a gelatin carrier gives the composition the ability to thermally

crosslink over a very small temperature range so that, for example, the composition can be easily extruded from a syringe at temperatures above 40°C, but still form a solid gel at physiologic temperature. The Wironen reference teaches that the gelatin component is used in the form of a solution having a 30-45% (w/w) gelatin concentration and further notes that the final gelatin content of the composition described is about 20-45% (w/w).

The Wironen reference specifically contrasts the teachings therein with a commercialized embodiment of the formulation described in the O'Leary reference. On page 3 of the Wironen reference, a commercially available embodiment of the O'Leary formulation is described as a "non-crosslinkable composition" comprising demineralized bone powder suspended in glycerol, which obviously would not exhibit the thermoreversible gelation property described in Wironen. Thus, the fundamental properties of the composition in Wironen are markedly different from the properties of the composition described in the O'Leary reference or the Yim reference, and Wironen itself suggests key distinctions between the O'Leary reference and the Wironen formulation. For this reason alone, there would be no motivation to combine the teachings of the Wironen reference with the O'Leary or Yim references.

Further, the specific language in the Wironen reference that discusses cancellous bone makes it clear that the reference only suggests the addition of such a component to the gelatin based composition described therein. Specifically, the reference suggests that "[t]he composition according to this invention...may act as a carrier for cortical, cancellous, or cortical and cancellous bone chips." (page 13, lines 11-14)(emphasis added). The reference goes further to suggest that "such compositions are useful for fulfilling larger bone voids." (page 13, line 14)(emphasis added). Thus, it is clear that the Wironen reference only suggests the addition of cancellous bone to a gelatin based composition of the type described therein, meaning the composition exhibits thermoreversible gelation properties that are crucial to the invention described in Wironen.

Neither the O'Leary nor Yim references are directed to gelatin-based compositions exhibiting thermoreversible gelation characteristics. As explained above, Applicants respectfully submit that a fair reading of Wironen would only suggest to one of ordinary skill in the art that cancellous bone chips could be useful as an additive in a gelatin based composition that exhibits

thermoreversible gelation properties. For this additional reason, Applicants respectfully request that the Board overturn the sole rejection or record.

The Combined Teachings of the Cited Art Fail to Suggest Claims 23-30

Even if the references are properly combinable, which Applicants obviously do not admit as noted above, the resulting combination clearly fails to teach or suggest any of the compositions recited in Claims 23-30. Applicants note that each of Claims 23-30 recites a specific combination of ingredients at specific concentrations. For example, each of Claims 23-30 recite a specific concentration of cancellous bone in combination with specific concentrations of each additional ingredient. There is simply nothing in the Wironen reference, which is the only reference relied upon by the Examiner as being relevant to the use of cancellous bone, which suggests any of the claimed parts by weight with respect to cancellous bone.

The Wironen reference is completely silent as to any particular weight percent or parts by weight of cancellous bone. None of the examples in the Wironen reference describe a composition containing any amount of cancellous bone. As a result, Applicants submit that one of ordinary skill in the art would not find it obvious to form a composition as described in Claims 23-30, which each recite a specific combination of ingredients at specific concentrations.

Thus, Applicants respectfully note that at least one limitation of the claimed subject matter of Claims 23-30 is neither taught nor suggested in the cited art. To establish *prima facie* obviousness of a claimed invention, all the claimed limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). It has been noted repeatedly by the courts that "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 165 USPQ 494,496 (CCPA 1970). For this additional reason, Applicants respectfully submit that Claims 23-30 are patentable over the cited combination of references and request reconsideration and withdrawal of the rejection.

8. ***Claims Appendix***

An appendix containing a copy of the claims involved in the appeal.

CONCLUSION

In view of the foregoing arguments, Appellant respectfully submits that Claims 16-30 are patentable over the cited references. A decision from the Board of Patent Appeals and Interferences reversing the final rejection of the pending claims is therefore earnestly solicited.

Respectfully submitted,

Christopher M. Humphrey
Registration No. 43,683

CUSTOMER NO. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

"Express Mail" mailing label number EV 387069988 US
Date of Deposit December 15, 2004

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to:
Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Tracey S. Wright

APPENDIX

16. (Previously Presented) A bone graft substitute composition, comprising:
calcium sulfate;
demineralized bone matrix;
cancellous bone;
a plasticizing substance; and
a mixing solution.

17. (Previously Presented) The composition of claim 16, wherein the calcium sulfate comprises calcium sulfate hemihydrate.

18. (Previously Presented) The composition of claim 16, wherein the plasticizing substance comprises a cellulose derivative.

19. (Previously Presented) The composition of claim 16, wherein the plasticizing substance is selected from a group consisting of sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, ethylcellulose, hydroxyethylcellulose, and cellulose acetate butyrate.

20. (Previously Presented) The composition of claim 16, wherein the mixing solution is selected from a group consisting of sterile water, inorganic salt, and cationic surface active agent.

21. (Previously Presented) The composition of claim 20, wherein the cationic surface active agent is selected from a group consisting of sodium chloride, phosphate buffered saline, potassium chloride, sodium sulfate, ammonium sulfate, ammonium acetate, and sodium acetate.

22. (Previously Presented) The composition of claim 16, wherein the mixing solution comprises sterile water.

23. (Previously Presented) The composition of claim 16, comprising:
about 80 to about 120 parts by weight of calcium sulfate;
about 10 to about 100 parts by weight of demineralized bone matrix;
about 10 to about 100 parts by weight of cancellous bone;
about 1 to about 40 parts by weight of a plasticizing substance; and
about 21 to about 250 parts by weight of a mixing solution.

24. (Previously Presented) The composition of claim 16, comprising:
about 90 to about 110 parts by weight of calcium sulfate;
about 10 to about 50 parts by weight of demineralized bone matrix;
about 15 to about 50 parts by weight of cancellous bone;
about 5 to about 20 parts by weight of a plasticizing substance;
about 80 to about 120 parts by weight of a mixing solution.

25. (Previously Presented) The composition of claim 16, comprising:
about 98 to about 102 parts by weight of calcium sulfate;
about 13 to about 23 parts by weight of demineralized bone matrix;
about 27 to about 33 parts by weight of cancellous bone;
about 15 to about 20 parts by weight of a plasticizing substance; and
about 95 to about 105 parts by weight of a mixing solution.

26. (Previously Presented) The composition of claim 16, comprising:
about 100 parts by weight of calcium sulfate;
about 18 to about 19 parts by weight of demineralized bone matrix;
about 27 to about 28 parts by weight of cancellous bone;
about 17 to about 18 parts by weight of a plasticizing substance; and
about 101 to about 102 parts by weight of a mixing solution.

27. (Previously Presented) A bone graft substitute composition, comprising:

about 80 to about 120 parts by weight of calcium sulfate hemihydrate;
about 10 to about 100 parts by weight of demineralized bone matrix;
about 10 to about 100 parts by weight of cancellous bone;
about 1 to about 40 parts by weight of a carboxymethylcellulose; and
about 21 to about 250 parts by weight of sterile water.

28. (Previously Presented) The composition of claim 27, comprising:
about 90 to about 110 parts by weight of calcium sulfate hemihydrate;
about 10 to about 50 parts by weight of demineralized bone matrix;
about 15 to about 50 parts by weight of cancellous bone;
about 5 to about 20 parts by weight of carboxymethylcellulose; and
about 80 to about 120 parts by weight of sterile water.

29. (Previously Presented) The composition of claim 27, comprising:
about 98 to about 102 parts by weight of calcium sulfate hydrate;
about 13 to about 23 parts by weight of demineralized bone matrix;
about 27 to about 33 parts by weight of cancellous bone;
about 15 to about 20 parts by weight of carboxymethylcellulose; and
about 95 to about 105 parts by weight of sterile water.

30. (Previously Presented) The composition of claim 27, comprising:
about 100 parts by weight of calcium sulfate hemihydrate;
about 18 to about 19 parts by weight of demineralized bone matrix;
about 27 to about 28 parts by weight of cancellous bone;
about 17 to about 18 parts by weight of carboxymethylcellulose; and
about 101 to about 102 parts by weight of sterile water.